REMARKS

Claim amendments

Claims 1-6 and 38-60 are pending. Claim 39 has been amended to more clearly indicate that binding of the antibody or antigen binding fragment to ouabain is not inhibited by a concentration of digoxin, as high as 100μM. Support for the amendment can be found, for example, on page 22, lines 18-20 and Table 1 of the subject application.

Paragraph 5

Rejection of Claim 2, 5 and 6under 35 U.S.C. §101

Claims 2, 5 and 6 remain rejected under 35 U.S.C. §101 "for the reasons previously set forth in the Paper mailed March 3, 2004" (Office action, page 2). It is the Examiner's opinion that the "invention appears to be inoperative". The Examiner states that "[a]s drawn to the apparent typographical error of millimolar versus micromolar, the Declaration is convincing and the first Haupert Declaration will now be considered in light of the micromolar concentrations actually used" (Office Action, page 2).

Specifically, the Examiner is not persuaded by Dr. Haupert's statement that when "the inhibitor was digoxin at 50 and 100 micromolar the results were not statistically significant, indicating that the digoxin values clustered at the highest point in Figure 6 are in fact not different from zero inhibition" because "inhibition at 100 micromolar is not disclosed in Figure 6" and it is not clear that how "the 100 micromolar point was found, how statistical evaluation was done, and how many repetitions, how many datapoints used" (Office Action, page 3).

In the Second Declaration of Garnet T. Haupert, Jr., M.D. under 37 C.F.R. §1.132 (Dr. Haupert's Second Declaration), Dr. Haupert notes that the highest point of Figure 6 is 50 μM (Dr. Haupert's Second Declaration, paragraph 6). In the Declaration of Garnet T. Haupert, Jr., M.D. under 37 C.F.R. §1.132 (Dr. Haupert's First Declaration) Dr. Haupert clearly states how the statistical evaluation was done. Specifically, Dr. Haupert states that:

> *Because of the ambiguity in Figure 6 at the highest concentration of digoxin studied, we consulted the raw data in the laboratory notebook for this set of experiments, and applied a statistical analysis ("two-tailed T test") to determine the probability that the data points just above the zero line are in fact different*

from zero. At every concentration of digoxin tested, the absorbance value in the presence of that dose of digoxin was compared to the absorbance binding value in the absence of any inhibitor (total baseline binding), and the T test applied to determine statistically significant difference between the two values.

The generally accepted "p" value to indicate a statistically significant difference is $p \leq 0.05$. When the inhibitor was digoxin at 50 and 100 mM, the result was $p = 0.16\text{-}0.18$. This is well above the $p < 0.05$ level, indicating that the digoxin values clustered at the highest dose point in Figure 6 are in fact not different from zero inhibition (Dr. Haupert's First Declaration, paragraph 5, page 3).

The Examiner is not also not persuaded by Dr. Haupert's First and Second Declaration because "the studies are not commensurate in scope with the claimed invention which claims no cross reactivity at 100 micromolar digoxin" (Office Action, page 3). Finally, the Examiner is also not persuaded that "the absence of cross-reactivity was also documented by equilibrium saturation binding" in the Parhami-Seren *et al., J. Immunol.* reference because "a review of the cited reference reveals that the concentrations of digoxin tested were in the nM, not the micromolar range" (Office Action, page 3) and invites Applicants to submit "objective evidence demonstrating that binding of antibody 1-10 and by extension 7-1 . . . are not inhibited by a concentration of digoxin as high as 100 micromolar" (Office Action, page 4).

In the specification as filed, Applicants have provided additional, objective evidence demonstrating that binding of antibodies 1-10 and 7-1 are not inhibited by a concentration of digoxin as high as 100 micromolar. As noted in the Dr. Haupert's Second Declaration, in Table 1 of the application as filed Applicants found an IC_{50} (μM) reading of "NI" (NI: No inhibition was observed at highest inhibitor concentration (100μM)) for antibodies 1-10 and 7-1 in the presence of digoxin(specification, Table 1, page 29, and Table 1 legend, page 30). Upon discussing the results in Table 1, Applicants clearly teach that:

> three mAbs showed minimal (5A12) or absent (7-1 and 1-10) cross reactivity with Dig, as their binding to Oua-BGG could not be inhibited with concentrations as high as 100 μM of free Dig (specification, page 22, lines 18-20).

Clearly, Applicants' claimed 1-10 or 7-1 monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain and for the ouabain component of a

ouabain-carrier complex, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by a concentration of digoxin as high as 100μM is operative.

Paragraph 6

Rejection of Claims 2, 5 and 6 under 35 U.S.C. §112, first paragraph

Claims 2, 5 and 6 remain rejected under 35 U.S.C. §112, first paragraph "for the reasons previously set forth in the Paper mailed March 3, 2004" (Office Action, page 4). It is the Examiner's opinion that since the embodiments are inoperative, one of skill in the art would not know how to make and use the invention.

Applicants respectfully disagree. As noted above, the subject matter of Applicants' claimed invention is clearly operative. In addition, Applicants have shown how to make and use the 1-10 or 7-1 monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain and for the ouabain component of a ouabain-carrier complex, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by a concentration of digoxin as high as 100μM.

Thus, Applicants have provided an enabling disclosure for the full scope of the claimed invention.

Paragraph 7

Rejection of Claim 39 under 35 U.S.C. §102(b)

Claim 39 is rejected under 35 U.S.C. §102(b) "for the reasons previously set forth in the Paper mailed March 3, 2004" (Office Action, page 4). The Examiner states that Lin *et al.* "specifically teach, in a competition assay that both antigen and antigen-enzyme conjugate (which is a ouabain-carrier complex) compete for binding to the primary ouabain antibody in the plate", and thus, "the prior art antibody binds to both free antigen and ouabain-carrier complex" (Office Action, page 4). The Examiner notes that Applicants' argument that "Lin et al do not teach that the monoclonal antibody has binding specificity for ouabain and for the ouabain component of a ouabain-carrier complex" is not persuasive "for the reasons set forth above and further, it is noted that Applicant is arguing limitations not recited in the claims as currently constituted" (Office Action, page 5).

Applicants respectfully disagree. As previously amended, Claim 39 is drawn to a monoclonal antibody produced by a method "wherein the antibody or antigen binding fragment thereof ***has binding specificity for ouabain and for the ouabain component of a ouabain-carrier complex***" (Claim 39, emphasis added). Furthermore, Lin *et al.* clearly do not teach a monoclonal antibody produced by a method in which a mammal is immunized ***with ouabain bound to an antibody which has binding specificity for a glycoside*** (Claim 39, step a). Finally, Claim 39 has been amended to more clearly indicate that binding of the antibody or antigen binding fragment to ouabain is not inhibited by a concentration of digoxin, as high as 100μM.

Lin *et al.* clearly do not teach Applicants' claimed invention, particularly as amended.

Paragraph 8

Rejection of Claim 39 under 35 U.S.C. §103

Claim 39 is rejected under 35 U.S.C. §103 "for the reasons previously set forth in the Paper mailed March 3, 2004" (Office Action, page 5). The Examiner states that Applicants' argument in the previously filed Amendment has not been found persuasive "because the claim is not drawn to a monoclonal antibody that is not inhibited by 100 micromolar digoxin" (Office Action, pages 5-6).

As indicated above, Claim 39 has been amended to more clearly indicate that binding of the antibody or antigen binding fragment to ouabain is not inhibited by a concentration of digoxin, as high as 100μM, thereby obviating the rejection.

Paragraph 9

Rejection of Claims 2, 5, 6, 41-43, 45-55 and 57-59 under 35 U.S.C. §112, first paragraph

Claims 2, 5, 6, 41-43, 45-55 and 57-59 remain rejected under 35 U.S.C. §112, first paragraph "for the reasons previously set forth in the Paper mailed March 3, 2004" (Office Action, page 6). The Examiner states that the Statement Under 37 C.F.R. § 1.805(a) submitted on December 24, 2003 "appears to be limited to circumstances drawn only to pendency of the subject application, application for reissue patent or reexamination proceedings" (Office Action, page 6). The Examiner states that the "statement cannot be limited only to pendency of the subject application, application for reissue patent or reexamination proceedings" and that "an

affidavit or declaration stating that the deposit will be replaced if viable samples cannot be dispensed by the depository is required" (Office Action, page 7).

Applicants are filing concurrently a Declaration that the deposit will be replaced if viable samples cannot be dispensed by the depository, thereby obviating the rejection.

Paragraph 10

Rejection of claims 1, 3, 4 and 38 under 35 U.S.C. §112, first paragraph

Claims 1, 3, 4 and 38 remain rejected under 35 U.S.C. §112, first paragraph "as the specification does not contain a written description of the claimed invention" (Office Action, page 7). The Examiner states that "in the absence of the limitations drawn to antibodies 7-1 and 1-10, no support is found for the broadly worded claims drawn to any monoclonal antibody or antigen binding fragment thereof that binds ouabain but is not inhibited at said concentration, no support for the broadly worded claims drawn to any monoclonal antibody or antigen binding thereof that binds to ouabain component of a ouabain-carrier complex and is not inhibited at said concentration of digoxin" (Office Action, pages 7-8). It is the Examiner's opinion that the "subject matter claimed in claims 1, 3-4, 38 broadens the scope of the invention as originally disclosed in the specification" (Office Action, page 8).

Applicants respectfully disagree. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention (*Vas-Cath, Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111,1116 (Fed. Cir. 1991)). The court has further stated that the "PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims"(*In re Wertheim*, 191 U.S.P.Q. 90, 97 (Fed. Cir. 1976)). Possession may be shown by a description in the specification of an actual reduction to practice of the claimed method (MPEP 2163). For a genus, the written description requirement may be satisfied through sufficient description of a representative number of species by actual reduction to practice (MPEP 2163).

In the specification as filed, Applicants clearly teach and claim "a monoclonal antibody (mAb) or antigen binding fragment thereof having binding specificity for ouabain, wherein the antibody or antigen binding fragment does not crossreact with digoxin" (specification, page 8,

lines 7-9, original Claim 1). The court has clearly stated that there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed (*In re Wertheim* 191 U.S.P.Q. 90.97 (CCPA 1976)). Present Claims 1, 3, 4 and 38 are not broader than original Claim 1.

In addition, Applicants have clearly shown possession of the claimed invention by reducing the invention to practice. That is, Applicants have provided a method for producing a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain and for the ouabain component of a ouabain-carrier complex, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by a concentration of digoxin as high as 100μM, and have reduced the invention to practice by producing a representative number of such monoclonal antibodies (*i.e.,* 1-10 and 7-1) having the claimed properties. Other monoclonal antibodies having the claimed properties can be produced using Applicants' method. Methods for assessing whether binding of the antibody produced by Applicants' method to ouabain is not inhibited by a concentration of digoxin as high as 100μM are also provided in the subject application. The Examiner has not presented any evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.

Clearly, Applicants have met the written requirement description requirement for the claimed subject matter.

Paragraph 11

Rejection of Claims 40-44 under 35 U.S.C. §112, first paragraph

Claims 40-44 remain rejected under 35 U.S.C. §112, first paragraph "as the specification does not contain a written description of the claimed invention" (Office Action, page 8). The Examiner states that the limitations of binding of a monoclonal antibody or an antibody binding fragment thereof having binding specificity for ouabain and for the ouabain component of a ouabain carrier complex which is not inhibited by a concentration of digoxin as high as 25 micromolar has no clear support in the specification and the claims as originally filed" (Office Action, page 8). The Examiner notes Applicants position that support can be found in Table 1 and Figure 3 of the subject application. However, it is the Examiner's opinion that "Figure 3 discloses support for inhibition of antibody binding to ouabain-BGG by approximately 10^{-5}

micromolar Digoxin for three antibodies, antibodies, 5A12, 7-1 and 1-10" and a "further search of the specification did not reveal any statement drawn to concentrations 'as high as 25 micromolar'" (Office Action, page 8).

Applicants respectfully disagree. There is no *in haec verba* requirement for new or added claim language and such language can be supported in the specification through express, implicit or inherent disclosure (MPEP 2163). The x axis of Figure 3 clearly indicates a monoclonal antibody or antigen binding fragment thereof which has binding specificity for ouabain and for the ouabain component of a ouabain-carrier complex, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by a concentration of digoxin as high as 25μM (*e.g.*, 5A12).

In addition, Applicants are confused by the Examiner's interpretation of Figure 3 and respectfully request clarification. In Figure 3, the shaded squares represent antibody 5A12, the shaded triangles represents antibody 7-1 and the open triangle represents antibody 1-10. Applicants fail to see where it is shown in Figure 3 that binding of antibody 5A12, 7-1 or 1-10 to ouabain-BGG is inhibited by approximately 10^{-5} micromolar Digoxin.

Finally, Applicants have clearly shown possession of the claimed invention by reducing the invention to practice. That is, Applicants have provided a method for producing a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain and for the ouabain component of a ouabain-carrier complex, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by a concentration of digoxin as high as 25μM, and have reduced the invention to practice by producing a representative number of such monoclonal antibodies (*i.e.*, 5A12) having the claimed properties. Other monoclonal antibodies having the claimed properties can be produced using Applicants' method. Methods for assessing whether binding of the antibody produced by Applicants' method to ouabain is not inhibited by a concentration of digoxin as high as 25μM are also provided in the subject application. The Examiner has not presented any evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.

Clearly, Applicants have met the written requirement description requirement for the claimed subject matter.

Paragraph 12

Rejection of Claims 56 and 60 under 35 U.S.C. §112, first paragraph

Claims 56 and 60 are rejected under 35 U.S.C. §112, first paragraph "as the specification does not contain a written description of the claimed invention" (Office Action, page 8). The Examiner states that "the newly added limitation" of Claims 56 and 60, "in the absence of reference to 8E4 represents new matter" (Office Action, page 9).

Applicants respectfully disagree. Applicants have clearly shown possession of the claimed invention by reducing the invention to practice. That is, Applicants have provided a method for producing a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain and for the ouabain component of a ouabain-carrier complex, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by a concentration of digoxin as high as 50μM, and have reduced the invention to practice by producing a representative number of such monoclonal antibodies (*i.e.,* 8E4) having the claimed properties. Other monoclonal antibodies having the claimed properties can be produced using Applicants' method. Methods for assessing whether binding of the antibody produced by Applicants' method to ouabain is not inhibited by a concentration of digoxin as high as 50μM are also provided in the subject application. The Examiner has not presented any evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.

Clearly, Applicants have met the written requirement description requirement for the claimed subject matter.

Paragraph 13

Rejection of Claim 39 under 35 U.S.C. §112, first paragraph

Claim 39 is rejected under 35 U.S.C. §112, first paragraph "as lacking an adequate written description" (Office Action, page 9). The Examiner states that "[a]lthough the specification discloses a single antibody which has binding specificity for a glycoside, anti-digoxin 26-10 mAb, which when bound to ouabain and used as an immunogen produces antibodies which cross react with digoxin at greater than 25, 50, 70 micromolar, none of the produced antibodies have been shown to 'not crossreact with digoxin', and thus this does not

provide a description of antibody which has binding specificity for a glycoside that when bound to ouabain makes antibodies having specificity for ouabain and which do not cross react with digoxin that would satisfy the standard set out in Enzo" or Lilly (Office Action, page 12).

As noted above, Applicants have clearly shown possession of the claimed invention by reducing the invention to practice. That is, Applicants carried out the claimed method for producing a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain and for the ouabain component of a ouabain-carrier complex, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by a concentration of digoxin as high as 100μM, and have reduced the invention to practice by producing a representative number of such monoclonal antibodies (*i.e.*, 1-10 and 7-1) having the claimed properties.

In order to more clearly define the invention, Claim 39 has been amended to indicate that binding of the antibody or antigen binding fragment to ouabain is not inhibited by a concentration of digoxin, as high as 100μM, thereby obviating the rejection.

Paragraph 14

Rejection of Claims 38, 44 and 60 under 35 U.S.C. §112, first paragraph

Claims 38, 44 and 60 are rejected under 35 U.S.C. §112, first paragraph "as failing to comply with the enablement requirement" (Office Action, page 13). The Examiner states that "implicit in the recitation of a 'pharmaceutical' composition is the *in vivo* use thereof for treatment" (Office Action, page 13). The Examiner states that Parharmi-Seren *et al., J. Immunol.* 1999 "specifically teach that, at the time the invention was made that 'in mammals, Oua and OLC **may** (emphasis added) play a role in the regulation of sodium balane, arterial pressure and smooth muscle tone and have a pathophysiological role in common clinical disorders" (OFfice Action, pages 14-15). The Examiner further states that "[g]iven that it was unknown what role in fact was played by these molecules, one could not predict and no one of skill would beleive it more likely than not that the claimed invention would function as contemplated or implied as pharmaceutical composition" (Office Action, page 15).

Applicants respectfully disagree, and respectfully request that the Examiner provide support for the implicit definition of the term "pharmaceutical". A pharmaceutical refers to the practice or preparing and dispensing drugs (Stedman's Medical Dictionary, 26th edition). A

pharmaceutical is suitable for administration *in vivo* such as suitable for administration to an animal. However, administration of a pharmaceutical to an animal does not necessarily have to be for treatment purposes. The pharmaceutical composition for administration to an animal can also be used to study and verify a role for ouabain as Applicants teach in the specification. In addition, Applicants also clearly teach methods of producing the claimed pharmaceutical compositions on page 15, line 20 - page 16, line 17.

Applicants have clearly provided an enabling disclosure for the full scope of the claimed invention.

Paragraph 15

Rejection of Claim 39 under 35 U.S.C. §112, first paragraph

Claim 39 is rejected under 35 U.S.C. §112, first paragraph "as failing to comply with the enablement requirement" (Office Action, page 16). The Examiner states that "although the specification teaches that the invention relates to monoclonal antibodies, i.e., 1-10, 5A12, 7-1 8E4 or antigen binding fragments thereof having binding specificity for ouabain, wherein the antibody or antigen binding fragment does not cross react with digoxin . . . the exmplified antibodies produced by the exemplified process cross-react with digoxin" (Office Action, pages 16-17).

As noted above, Applicants have clearly shown possession of the claimed invention by reducing the invention to practice. That is, Applicants carried out the claimed method for producing a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain and for the ouabain component of a ouabain-carrier complex, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by a concentration of digoxin as high as 100μM, and have reduced the invention to practice by producing a representative number of such monoclonal antibodies (*i.e.*, 1-10 and 7-1) having the claimed properties.

In order to more clearly define the invention, Claim 39 has been amended to indicate that binding of the antibody or antigen binding fragment to ouabain is not inhibited by a concentration of digoxin, as high as 100μM, thereby obviating the rejection.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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